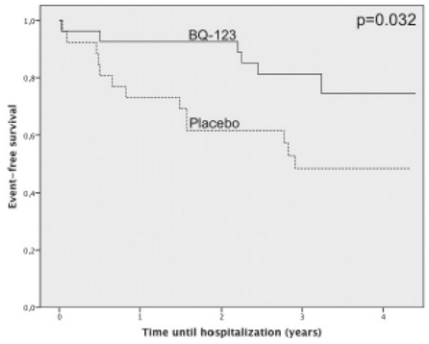
with patients randomized to placebo (3.8 years (95% CI: 3.3–4.2) for BQ-123 versus 2.8 years (2.1-3.4) for placebo, p = 0.032, Figure 1). Conclusion: Short-term administration of BQ-123 in patients undergoing primary PCI for STE-ACS leads to a longer cardiovascular event-free survival.



doi:10.1016/j.lfs.2014.01.034

Clinical features between heart failure and sleep disordered breathing

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Introduction: Little has been known about clinical background of the patients with heart failure (HF) and sleep disordered breathing (SDB). The aim of this study was to elucidate the relationship between HF and SDB. Methods: 1121 patients admitted to our institute with the diagnosis of HF between 2006 and 2012 was enrolled. SDB was defined >5/h of apnea–hypopnea index (AHI). Obstructive sleep apnea (OSA) group and central sleep apnea (CSA) group were defined based on the data of type III sleep monitor (Morpheus). Results: Among 1121 patients 328 (29%) underwent screening of type III sleep monitor. In the 328 patients, 275 (84%) patients showed SDB. Among these 275 SDB patients, 135 (41%) were OSA, and 140 (43%) were CSA. AHI was significantly higher (OSA: 22.5 ± 16.2, CSA: 29.8 ± 14.9, $P < 0.05$) and ejection fraction (EF) was significantly lower (OSA: 40.1 ± 17.1%, CSA: 33.5 ± 14.1%, $P < 0.05$) in CSA group between two groups. Among 140 CSA patients, 80 (57%) patients have heart failure with reduced ejection fraction (HFREF) and among 135 OSA patients, 60 (44%) patients have HFREF. Conclusions: SDB was highly associated with HF and the clinical features between OSA and CSA with HF were different. CSA patients were associated with lower EF and higher AHI than OSA patients. This study suggested that SDB was one of an important target of treatment HF and to treat HF according to these clinical subsets of SDB was clinically required in the future.

doi:10.1016/j.lfs.2014.01.035

Selective deletion of endothelin B receptors from vascular smooth muscle does not inhibit neointimal lesion formation

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Pharmacological inhibition and genetic deletion (Murakoshi et al., 2002; Kirkby et al., 2012) suggest that endothelin (ET) A-selective antagonists are preferable to mixed ETA/B antagonists for prevention of neointimal lesion formation. ETB receptors expressed in smooth muscle cells may, however, contribute to lesion development. It was proposed that ETB deletion from smooth muscle (SM) would reduce lesion formation following arterial injury. Methods: Mice bearing a floxed ETB gene or expressing cre-recombinase under the SM22 promoter were crossed to produce SM-selective ETB deletion. SMETB knockout mice were identified by genotyping and backcrossed to C57Bl/6J (4–6 generations). Functional confirmation of ET deletion was determined by exposing trachea, and mesenteric artery and vein, to sarafotoxin 6c in a myograph. Femoral injury was performed in adult, male SMETB knockout mice and littermate controls and arteries were harvested 33 days later for structural analysis. Results: SMETB knockout reduced (~55%), but did not abolish, ETB-mediated contraction in trachea. In contrast, S6c-mediated contraction in mesenteric veins (130 + 46% KPSS, n = 4), and in mesenteric arteries cultured for 24 h (72 + 24% KPSS, n = 4), was abolished by SMETB deletion (5.1 + 3.4% KPSS and 0% KPSS, respectively). Femoral artery injury produced large, neointimal lesions (47.4 + 10.6%; n = 7) but SMETB knockout did not alter lesion size (42.2 + 4.5%; n = 9; P = 0.64). Conclusions: Stimulation of ETB receptors in SM does not influence neointimal lesion formation. This supports the suggestion that ETA-selective antagonists are preferable to non-selective antagonists for prevention of neointimal proliferation. The study was funded by the BHF (project grant and CoRE). Murakoshi et al. (2002) Circulation 106:15; Kirkby et al. (2012) Cardiovasc Res, 95, 19.

doi:10.1016/j.lfs.2014.01.036

P-116

Neointimal lesion formation does not induce endothelin (ET) B-mediated contraction in murine femoral arteries

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Incubation of arteries ex vivo induces ETB-mediated contraction (Adner et al., 1998), possibly via transcriptional mechanisms (Skovsted et al., 2012). ETB receptors are also expressed in neointimal lesions (Azuma et al., 1994). It was proposed that ETB-mediated contraction would be induced by neointimal lesion formation. Methods: Femoral arteries from adult, male C57Bl/6J mice (n = 6) were harvested 36 +/− 2 days after ligation. Isolated mesenteric and femoral veins and arteries from uninjured mice were cultured (DMEM; 37 °C; 5% CO_2; 5 days) before analysis in a myograph. Contractile function was assessed using phenylephrine (10^{-9}–3×10^{-5} M), endothelin-1 (10^{-11}–10^{-7}M) and sarafotoxin 6c (10^{-11}–10^{-7}M). Relaxant function was assessed using endothelium-dependent (acetylcholine; 10^{-9}–3×10^{-5} M) and independent (sodium nitroprusside; 10^{-9}–3×10^{-5}M) agents after contraction with phenylephrine. Results: Freshly isolated mesenteric veins contracted in response to S6c whereas mesenteric arteries and femoral veins did not. Some (4/10) femoral arteries produced small S6c-induced contractions (21.86 +/− 3.72% KPSS,

n = 4). Incubation induced ETB-mediated contraction in mesenteric, but not in femoral arteries. Arterial ligation had little effect on contractile or relaxant function of murine femoral arteries and did not induce a contractile response to S6c. Conclusions: Neointimal lesion formation did not induce S6c-mediated contraction in mouse femoral arteries, possibly because ETB receptor activity cannot be induced in this artery. These data do not support the need for mixed ETA/ETB antagonists for inhibition of neointimal lesion formation. The study was supported by the BHF (project grant and CoRE). Adner et al. (1998) Acta Physiol Scand, 163,121; Azuma et al. (1994) Am J Physiol, 267, H2259; Skovsted et al. (2012) Life Sci, 91, 593.

doi:10.1016/j.lfs.2014.01.037

Smooth muscle specific disruption of the endothelin A receptor in mice reduces arterial pressure and affects vascular development

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The role of vascular smooth muscle endothelin A receptors (ETA) in development and normal physiology remains incompletely understood. To address this, mice were generated with smooth muscle-specific knockout (KO) of ETA. Mice were homozygous for loxP-flanked exons 6–8 of the ETA gene (floxed) or were also hemizygous for a transgene expressing Cre recombinase under control of the smooth muscle-specific SM22 promoter (KO mice). Genotyping at 17 days postnatal yielded a 5:1 ratio of floxed: KO mice. Smooth muscle actin staining of embryos at day E9.5 revealed increased tortuosity in dorsal aortae. Mice surviving to weaning developed and bred normally. ETA KO mice aged 2–3 months manifested EDNRA gene recombination in all organs tested. Aortas from KO mice had a >90% reduction in ETA mRNA content, but no differences between genotypes in ET-1 or ETB mRNA levels. The addition of 0.01–100 nM ET-1 to isolated femoral arteries from floxed, but not KO, mice dose-dependently decreased vessel diameter (up to 80% reduction in the presence of ETB blockade). Intravenous infusion of ET-1 into floxed, but not KO, mice acutely increased mean arterial pressure (MAP) (by ~10 mm Hg). Telemetric analysis revealed decreased MAP in KO mice (by ~7–10 mm Hg); this MAP reduction was evident on normal and high salt diets. In conclusion, ETA is important for vascular development and is involved in the maintenance of arterial pressure under physiological conditions.

doi:10.1016/j.lfs.2014.01.038

Plasma endothelin-1 level is a predictor of 10-year mortality in a general population: The Tanushimaru study

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Background: Endothelin-1 (ET-1) is a potent vasoconstrictor and an elevated plasma level is a prognostic marker in patients with cardiovascular diseases and/or malignancies. We hypothesized that an elevated plasma level might be a prognostic marker even in subjects without apparent cardiovascular disease or malignancy at baseline. Methods and results: We measured plasma ET-1 levels in 1440 healthy subjects over 40 years of age (580 men, 860 women) who were periodically followed for 10 years. The follow-up rate was 96.8%. Baseline plasma ET-1 levels were categorized into quartiles. Baseline plasma ET-1 levels were significantly associated with age, blood pressure, high-density lipoprotein-cholesterol, renal function, uric acid and all-cause death, but not with cardiovascular or cancer death. Kaplan–Meier curves demonstrated that all-cause mortality was significantly higher in the highest quartile of ET-1 than in the lowest quartile. Cox proportional hazards regression analysis demonstrated that ET-1 was an independent predictor of all-cause death [hazard ratio: 1.11, 95% confidence interval (CI) 1.01–1.23 per 1 pg/ml difference]. The hazard ratio of all-cause death in the highest quartile of plasma ET-1 (>5.9 pg/ml) vs. the lowest quartile after adjusting for confounding factors was 1.54 (95% CI 1.09–2.20). Conclusions: The plasma ET-1 level may be a predictor of all-cause death in a healthy population.

doi:10.1016/j.lfs.2014.01.039

Potential association between circulatory level of endothelin-1 and metabolic syndrome in Bangladeshi rural women: A population-based cross-sectional study

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Background: Metabolic alterations and endothelial dysfunction are interrelated processes in type 2 diabetes and metabolic syndrome (MetS) that often develop in parallel. In this study we assessed the association of vasoactive peptide, endothelin-1 (ET-1) with MetS conducted in a study in rural Bangladeshi women. Design and methods: Plasma level of ET-1 was measured by ELIZA and MetS was defined according to the criteria of NCEP-ATP III. Logistic regression was used to examine the association between circulatory ET-1 level and MetS and its components. Results: A total of 1485 rural Bangladeshi women aged >15 years were studied using a population based cross-sectional survey. The prevalence rate of MetS was 25.05% (NCEP ATP III). Mean values of BMI, waist circumference, blood pressure (SBP, DBP), plasma level of fasting glucose, triglyceride, HDL, cholesterol, insulin and vascular endothelial growth factor were significantly higher in MetS group compared to non-MetS group. ET-1 levels were significantly increased in MetS subjects (MetS vs. non-MetS: 4.32 ± 0.24 vs. 3.41 ± 0.18, $p = 0.003$). In multivariable analyses, we found that ET-1 had significant positive associations with DBP (beta = 0.051, $p = 0.001$) and SBP (beta = 0.028, $p < 0.001$) even after adjusting for age. We also found that mean plasma levels of ET-1 increased in direct proportion to levels of MetS components. Conclusions: We here demonstrate for the first time that in Bangladeshi rural women, plasma level of ET-1 is related to MetS and its components, suggesting a possible role of ET-1 as a surrogate biomarker for the disease and its complications. This is the first study assessing ET-1 in Mets subjects from a South Asian country.

doi:10.1016/j.lfs.2014.01.040